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L13: Entry 61 of 260

File: PGPB

Nov 11, 2004

DOCUMENT-IDENTIFIER: US 20040224010 A1

TITLE: Ophthalmic liposome compositions and uses thereof

Current US Classification, US Primary Class/Subclass:
424/450Detail Description Paragraph:

[0010] In one embodiment, the lipid phase comprises a neutral lipid as well as a cationic lipid or a mucoadhesive compound. Suitable neutral lipids include any of a number of lipid species which exist either in an uncharged or neutral zwitterionic form at physiological pH. Such neutral lipids include, but are not limited to, phospholipids, such as phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, palmitoyloleoyl phosphatidylcholine, lysophosphatidylcholine, lysophosphatidylethanolamine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, distearoylphosphatidylcholine and dilinoleoylphosphatidylcholine. In a preferred embodiment, the neutral lipid is a phosphatidylcholine, such as Phospholipon 90H, Phospholipon 80H or a mixture thereof. In another preferred embodiment the phospholipid includes, but is not limited to, phosphatidyl choline (PC), lyso-phosphatidyl choline (l-PC), phosphatidyl serine (PS), phosphatidyl ethanolamine (PE), phosphatidyl glycerol (PG), and phosphatidyl inositol (PI). Suitable cationic lipids include those that carry a net positive charge at physiological pH. Such cationic lipids include, but are not limited to, N,N-dioleoyl-N,N-dimethylammonium chloride ("DODAC"); N-(2,3-dioleoyloxy)propyl-N,N,N-triethylammonium chloride ("DOTMA"); N,N-distearyl-N,N-dimethylammonium bromide ("DDAB"); N-(2,3-dioleoyloxy)propyl-N,N,N-trimethylammonium chloride ("DOTAP"); 3.beta.-(N-(N',N'-dimethylaminoethane)-carbamoyl)cholesterol ("DC-Chol"), N-(1-(2,3-dioleoyloxy)propyl)-N-2-(sperminecarboxamido)ethyl-N,N-dimethyl- ammonium trifluoroacetate ("DOSPA"), dioctadecylamidoglycyl carboxyspermine ("DOGS"); 1,2-dioleoyl-sn-3-phosphoethanolamine ("DOPE"); N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide ("DMRIE"); stearylamine; dimethyldioctadecylammonium bromide; and 3B-[N',N'-dimethylaminoethane)-carbamol. In a preferred embodiment, the cationic lipid is, for example, stearylamine, DC-Cholesterol, dimethyldioctadecylammonium bromide, or 3B-[N',N'-dimethylaminoethane)-carbamol. Suitable mucoadhesive compounds include, but are not limited to, Carbopol 934 P, polyaxomers, carbomers and plant lectins.

Detail Description Paragraph:

[0013] In another embodiment, the lipid formulation further comprises a modifying agent including, but not limited to, cholesterol, stearylamine, cholesteryl hemisuccinate, phosphatidic acids, dicetyl phosphate and fatty acids.

Detail Description Paragraph:

[0049] Various biologically inactive, mucoadhesive compounds or cationic lipids can be added to the following basic formulation and screened for their ocular residence time: Liposomes will be made up in 0.06 M boric acid buffer (pH 7.2) using 0.1% (w/v) phosphatidyl choline (Phospholipon 90-H), 0.1% (w/v) Sodium diclofenac, and either 0.0025% (v/v) benzalkonium chloride or 0.05% (w/v) chlorobutanol as a preservative. The ratio of cationic lipid to neutral phosphatidyl choline can be

varied, and cationic lipids included in the liposomes to be tested include, but are not limited to, stearylamine, DC-Cholesterol, dimethyldioctadecylammonium bromide, or 3B-[N',N'-dimethylaminoethane)-carbamol. Alternatively, mucoadhesive compounds (examples: Carbopol 934 P, Polyaxomers, Carbomers, or plant lectins) can be incorporated into the liposomes of the present invention.

CLAIMS:

4. A lipid formulation in accordance with claim 2, wherein said phospholipid is a member selected from the group consisting of phosphatidylglycerols (PG), phosphatidylethanolamines (PE), phosphatidylserines (PS) and hydrogenated phosphatidylcholines (PC).

8. A lipid formulation in accordance with claim 7, wherein said cationic lipid is a member of the group consisting of stearylamine, DC-Cholesterol, dimethyldioctadecylammonium bromide, or 3B-[N',N'-dimethylaminoethane)-carbamol.

23. A lipid formulation in accordance with claim 1, further comprising a modifying agent selected from the group consisting of cholesterol, stearylamine, cholesteryl hemisuccinate, phosphatidic acids, dicetyl phosphate and fatty acids.

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L13: Entry 64 of 260

File: PGPB

Oct 28, 2004

DOCUMENT-IDENTIFIER: US 20040213766 A1

TITLE: Compositions and methods for treating transplants

Current US Classification, US Secondary Class/Subclass:
424/450

Summary of Invention Paragraph:

[0019] Since the lipids of FUVs are incorporated into the membranes of the target cells, functional features of cell membranes may be modified at will. For example, FUVs carrying phosphatidylserine can modify the surface of T cells such that they masquerade as apoptotic cells to macrophages in culture (Borisenko et al., 2003; Fadok et al., 2001).

Detail Description Paragraph:

[0109] A raft former is a compound which will sit within the lipid layer of a vesicle when the vesicle is in an aqueous solution, and will form or cause formation of discrete regions within the vesicle wall (also known as rafts). These discrete regions tend to destabilize the vesicle, increasing its fusogenicity. Examples of raft formers are cholesterol (formula XXIV), sphingomyelin, and proteins and polypeptides known to be membrane bound. Fusogenicity may also be enhanced by selecting polar lipids, which will result in a surface charge on the vesicle, which is the opposite of the charge of the Gouey-Chapman layer of the target cells (typically the Gouey-Chapman layer is positively charged).

Detail Description Paragraph:

[0110] Examples of polar lipids for use in the present invention include 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) (formula XVII; a stable vesicle former), 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphate (POPA) (shown as the monosodium salt in formula XVIII), 1,2-dioleoyl-sn-glycero-3-ethylphosphocholine (DOPC-e) (shown as the chloride salt in formula XIX), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) (formula XX), 1,2-dioleoyl-sn-glycero-3-[phospho-1-serine] (DOPS) (shown as the sodium salt in formula XXI), 1-palmitoyl-2-docosahexaenoyl-sn-glycero-3-phosphocholine (formula XXII; a stable vesicle former), a typical sphingomyelin (formula mixture this sphingomyelin and DOPC), 1,2-dimyristoyl-sn-glycerol (formula polar lipids useful for the practice of the present invention include phosphatidyl serine (PS), phosphatidyl glycerol (PG), mixed chain phosphatidyl choline (MPC), phosphatidyl ethanol (PE), and phospholipids containing decosahexaenoic acids. Cit-DOPC and cit-DOPC-e are especially useful. Phosphatidylcholines, including those having a docosahexaenoic acid in the sn-1 and sn-2 positions (DHPC) may be used. Other diunsaturated lipids, such as diarachidonylphosphatidylcholine (for example 20:4 DOPC:DARPC), dilinolenoylphosphatidylcholine (for example 18:3 DOPC:DLNPC) are also useful. For example, DOPC may be mixed with increasing amounts of DLNPC, DARPC and DHPC during FUV preparation. Useful ratios include (DOPC:DLNPC, DARPC or DHPC) range from 1-1000:1, such as 25-500:1, including 1:1, 25:1, 50:1, 100:1, 500:1, and 1000:1. Combinations of phospholipids having large mean molecular areas can also be used, such as DOPC:DLNPC:DHPC. Diacylglycerol, a non-lamellar phase lipid, can also be mixed with DOPC. In addition, one can use polyethylene glycol (PEG) with weights of 20 repeats up to 4000 repeats.

Detail Description Paragraph:

[0133] Because the lipid composition of plasma membranes varies by cell type, the choice of cells for use in the assay is carefully considered, and should match as best the target cell type(s). For example, liver cell plasma membranes consist of about 7% phosphatidylethanolamine, while red blood cell plasma membranes contain 18% cit_bf(Alberts et al. 2002)cit_af ref_bf(Alberts, B. 2002 ref_num32)ref_af. Primary culture cells, as well as cell lines (available from the American Type Tissue Collection (ATCC); Manassus, Va.) are useful, although primary cultures are preferred because of the likelihood that the plasma membrane lipid composition is altered in transformed cells. Cell types include pancreas, intestinal, immune system, neuronal (including those of the brain, eye, nose and ear), lung, heart, blood, circulatory (lymph and blood), bone, cartilage, reproductive, glandular, enamel, adipose, skin, and hepatic. Cell lines include those derived from these tissues, such as Madin-Darby canine kidney (MDCK), Chinese hamster ovary (CHO), HeLa, etc. Cells may be from other organisms, such as plants, fungi (including yeasts), and bacteria. Examples of fusion rates with these other cell types include at least 100, 1000, 10.sup.4, 10.sup.5, 10.sup.6, 10.sup.7, 10.sup.8, 10.sup.9, 10.sup.10, and 10.sup.11 vesicle fusions/second. Unless otherwise specified, fusion rates are with respects to HUVECs under the conditions specified above. Fusion rates with respects to other cell types is for about 10.sup.6 cell, with a buffer, such as HBSS, and the vesicles are incubated with the cells for 120 minutes at 37.degree. C., 95% air/5% CO.sub.2, after which time residual vesicles are removed by washing the cells with buffer.

Detail Description Paragraph:

[0148] Plasma membranes contain lipid domains or rafts that are enriched in a particular lipid species. At the boundary of such a membrane raft are regions of dissimilar lipid species. These regions have the potential for instability, effecting how the membrane interacts with other membranes. Several phospholipids are known to increase lipid raft formation, including mixtures of phosphatidylcholines, sphingomyelin, and cholesterol. For example, DOPC, 18:0 sphingomyelin, and cholesterol are mixed in a 1:1:1 ratio during FUV preparation. Cholesterol preferentially partitions in the sphingomyelin phase, creating regions that are rich in DOPC and poor in cholesterol, and regions that are rich in sphingomyelin and rich in cholesterol.

Detail Description Paragraph:

[0238] To determine if vesicles were actually fusing with the cells or simply aggregating on the cell surface, HUVEC exposed to lipid vesicles and not removed from the culture wells were examined for the distribution of fluorescence by fluorescent microscopy. Cells exposed to all three compositions showed diffuse fluorescence throughout the cells after 60 minutes rather than punctate fluorescence, which would have suggested that lysosomes were sequestering the vesicles, thereby preventing cellular access to the carboxyfluorescein. Alternatively, the vesicles were aggregating on the cell surface. These results demonstrate that lipid vesicles fused to the cells and released the encapsulated contents within the cytoplasm rather than aggregating on the cell surface or being sequestered lysosomes.

Detail Description Paragraph:

[0309] Borisenko, G. G., T. Matura, S. X. Liu, V. A. Tyurin, J. Jianfei, F. B. Serinkan, and V. E. Kagan. 2003. Macrophage recognition of externalized phosphatidylserine and phagocytosis of apoptotic Jurkat cells--existence of a threshold. Arch.Biochem.Biophys. 413:41-52.

Detail Description Paragraph:

[0312] Fadok, V. A., A. de Cathelineau, D. L. Daleke, P. M. Henson, and D. L. Bratton. 2001. Loss of phospholipid asymmetry and surface exposure of phosphatidylserine is required for phagocytosis of apoptotic cells by macrophages and fibroblasts. J. Biol. Chem. 276:1071-1077.

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L13: Entry 255 of 260

File: USPT

Apr 4, 1989

DOCUMENT-IDENTIFIER: US 4818537 A

TITLE: Liposome composition for treating dry eye

Brief Summary Text (20):

The composition of the invention includes an aqueous suspension of liposomes whose lipid composition contains substantially saturated neutral vesicle-forming lipids, and between 10-40 mole percent of a quaternary benzyl amine having an aliphatic hydrocarbon chain of at least 12 carbon atoms. The aqueous medium is buffered to a preferred pH of between about 6.2 and 6.8, and may contain a bacteriostatic agent as well as a calcium-ion chelator, which acts to limit phospholipid hydrolysis, and further acts as a bacteriostatic agent. The liposomes composition may further include vitamin A and/or film forming lipids, such as long-chain fatty alcohols and cholesterol esters.

Drawing Description Text (4):

FIG. 3 shows the retention on an ocular tissue of HPC/BDSA SUVs formulated with 0 (closed circles), 10 (closed triangles), and 30 (open circles) mole percent of lysophosphatides and free fatty acids;

Detailed Description Text (5):

The liposomes of the composition can be formed from a variety of vesicle-forming lipids, which include dialiphatic chain lipids, such as phospholipids, diglycerides, and dialiphatic glycolipids, and cholesterol and derivatives thereof. The lipid components are present in an amount between about 60-90 of the total lipid components in the liposomes, the remainder being charged surface components described in the section below.

Detailed Description Text (6):

As defined herein, "phospholipids" include phosphatidic acid (PA) and phosphatidyl glycerol (PG), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS), plasmalogens, and sphingomyelin (SM). The term "cholesterol" is intended to encompass cholesterol derivatives such as: (3-hydroxy-5,6-cholestene) and related analogs, such as 3-amino-5,6-cholestene and 5,6-cholestene; cholestane, cholestanol and related analogs, such as 3-hydroxy-cholestane; and charged cholesterol derivatives such as cholesteryl .beta.-alanine and cholesteryl hemisuccinate. The term "glycolipid" as used herein is intended to encompass lipids having two fatty acid chains, one of which is the hydrocarbon chain of sphingosine, and one or more sugar residues. Examples of glycolipids suitable for practice of the present invention include cerebrosides, galactocerebrosides, glucocerebrosides, sulfatides and sphingolipids with di- and tri-saccharides as their polar head groups, i.e. di- and tri-hexosides.

Detailed Description Text (9):

In a preferred formulation, 30-90 mole percent of the total lipids are phospholipids; still more preferably, 60-90 mole % of the total lipids are saturated, neutral phospholipids such as hydrogenated phosphatidylcholine (HPC). Up to 40 mole % of of the total lipids may represent a saturated cholesterol derivative. The liposome composition illustrated in Examples I and II below, and in several of the subsequent examples, the vesicle-forming lipids include 80 mole percent HPC.

Detailed Description Text (11):

For treating dry eye conditions which are related to lack of tear-forming lipids, the liposome composition may be further formulated to include minor amounts of fatty alcohols, fatty acids, and/or cholesterol esters, with the proviso that these minor lipid components (a) do not significantly reduce the binding affinity of the liposomes for mucosal tissue and (b) are substantially unsaturated, and (c) are not toxic or irritating to the eye. The first proscription limits the amount of negatively charged lipid which can be included in the liposomes, and also limits the amount of lipid which is disruptive of lipid packing in the liposome bilayer.

Detailed Description Text (66):

SUVs containing 80 mole percent egg PC and 20 mole percent lysinyl phosphatidylethanolamine (lysinyl PE) were prepared as in Example II. Lysinyl PE is an amine-derivatized PE formed by coupling the free PE amine to the carboxyl group of lysine through an amide linkage, as detailed in the above-cited patent application for "Ophthalmic Liposomes". A portion of the SUV preparation was mixed with an equal volume of polymer solution containing 0.8% hydroxymethylcellulose and 0.2% polyvinylalcohol, and the remainder (control) was mixed with an equal volume of buffer solution.

Detailed Description Text (71):

To determine the effect of partially hydrolyzed liposomes on eye retention, BDSA SUVs prepared as in Example II were formulated to contain 0, 10, or 30 mole % of free fatty acids and lysophospholipids. The SUV suspensions were evaluated in the rabbit eye model described in Example III and IV. Results of the experiment are shown in FIG. 3, which plot retention of SUVs containing 0 (solid circles), 10 (solid triangles), and 30 (open circles) mole percent free fatty acids. The data show that the retention of the liposomes over a period of one hour was not affected by the content of fatty acids and lysophospholipids.

Detailed Description Text (79):

The extent of lipid hydrolysis, which results in the formation of lysophospholipids and free fatty acids, was determined as in Example VIII below. The results are shown in FIG. 5, where open triangle represent hydrolysis at pH 6.0; closed triangles, pH 6.8; open circles, pH 7.4; and closed circles, pH 8.0. As seen, the extent of hydrolysis is very sensitive to pH within the pH range tested.

Current US Original Classification (1):

424/450

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<u>L15</u> L14 and 424/450.ccls.	87	<u>L15</u>
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<u>L13</u> L12 and lyso\$	260	<u>L13</u>
<u>L12</u> L11 and 424/450.ccls.	420	<u>L12</u>
<u>L11</u> L10 and cholesterol	1225	<u>L11</u>
<u>L10</u> L9 and phosphatidylserine	1225	<u>L10</u>
<u>L9</u> L8 and phosphatidylethanolamine	1528	<u>L9</u>
<u>L8</u> L7 and cholesterol	2236	<u>L8</u>
<u>L7</u> (lecithin or phosphatidylcholine) same sphingomyelin	2983	<u>L7</u>
<u>L6</u> (lecithin or phosphatidylcholine) same sphingomyelin same phopshatidylethanolamine	0	<u>L6</u>
<u>L5</u> (lecithin or phosphatidylcholine) same sphingomyelin same phopshatidylethanolamine same cholesterol	0	<u>L5</u>
<u>L4</u> (lecithin or phosphatidylcholine) same spingomyelin same phopshatidylethanolamine	0	<u>L4</u>

<u>L3</u>	(lecithin or phosphatidylcholine) same spingomyelin same phopshatidylethanolamine same cholesterol	0	<u>L3</u>
<u>L2</u>	(lecithin or phosphatidylcholine) same spingomyelin same phopshatidylethanolamine same (phosphatidylserine) same (phosphatidylinositol) same cholesterol	0	<u>L2</u>
<u>L1</u>	(lecithin or phosphatidylcholine) same spingomyelin same phopshatidylethanolamine same (phosphatidyl adj1 serine) same (phosphatidyl adj1 inositol) same cholesterol	0	<u>L1</u>

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L15: Entry 83 of 87

File: USPT

Aug 19, 1997

DOCUMENT-IDENTIFIER: US 5658588 A
TITLE: Fibrinogen-coated liposomes

Brief Summary Text (13):

The present invention relates to a method for effectively incorporating fibrinogen onto the surface of liposome-like (e.g., cell membrane) structures or any amphiphilic or hydrophobic surface. It further encompasses the fibrinogen-coated liposome structures, themselves, and pharmaceutical compositions containing those structures. Those compositions can be used as platelet-like biochemical hemostats, drug delivery systems which target sites of inflammation and/or clotting, reagents for the imaging of clot-containing lesions, reagents for clinical, clot-based coagulation assays, a bioadhesive reagent to introduce molecules into cells or facilitate adhesion between chemical reactants, an adhesive reagent for facilitating chemical reactions between environmentally-incompatible reactants, a vaccine component or an adjuvant for vaccines, a reagent for modifying the lipid composition of biological membranes, and a reagent for transfection of genes into target cells.

Brief Summary Text (25):

Materials which can be used for forming liposomes are generally well known, as are the methods for their preparation. For example, any number of phospholipid or surfactant compounds may be used to form the liposomes. Representative of such compounds are phosphatidylcholine, both naturally occurring and synthetically prepared, phosphatidic acid, lysophosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, sphingolipids, phosphatidylglycerol, sphingomyelin, cardiolipin, glycolipids, gangliosides, cerebrosides, and the like, used either singly or intermixed such as in soybean phospholipids. In addition, other lipids, such as steroids, cholesterol, aliphatic amines, such as long chain aliphatic amines and carboxylic acids, long chain sulfates and phosphates, dicetyl phosphate, butylated hydroxy-toluene, tocopherol, retinol, and isoprenoid compounds may be intermixed with the phospholipid components to confer certain desired and known properties on the formed liposomes. Preferred liposome forming compounds used in the present invention include lecithin, cholesterol, and mixtures thereof.

Detailed Description Text (3):

Chemicals and Reagents--Human fibrinogen, grade L, from Kabi AB (Stockholm, Sweden) is desalted using gel permeation chromatography and then equilibrated in phosphate buffer containing 0.10M Na.sub.2 HPO.sub.4 and NaH.sub.2 PO.sub.4, pH 7.40, and 0.145M NaCl (PBS). This fibrinogen is stored at -20.degree. C. until use. The fibrinogen concentration of the solutions is determined using the molar absorptivity of the protein at 280 nm, 5.12.times.10.sup.5 M.sup.-1 cm.sup.-1. Before use, a frozen aliquot of fibrinogen is first thawed to room temperature and then heated to 37.degree. C. to dissolve any residual cryoprecipitate. For some experiments, the fibrinogen is uniformly labeled using Na.sup.125 I from Amersham (Arlington Heights, Ill.) and Iodo-Gen from Pierce (Rockford, Ill.) according to an established procedure. O-Phthaldialdehyde is from Sigma (St. Louis, Mo.). Palmitoyl chloride is from Aldrich (Milwaukee, Wis.). Egg yolk 1-.alpha.-lecithin from Avanti Polar Lipids (Birmingham, Ala.) and cholesterol from Fisher (Fair Lawn, N.J.) are dissolved in hexane:ethanol, 9:1, v/v, and stored under nitrogen at -20.degree. C. until use. 1-Palmitoyl-2-[(1-.sup.14 C)oleoyl-L-3-phosphatidylcholine ([.sup.14 C]

PC) Of specific activity 1.96 GBq-mmol.sup.-1 is from Amersham. Water is deionized and distilled using an all-glass apparatus. All other chemicals are of the highest quality available commercially.

Detailed Description Text (4):

Preparation Of Fibrinogen-Coated Liposomes--The method used to prepare fibrinogen-coated liposomes involves, first, the production of liposomes and, second, the palmitoylation of fibrinogen in the presence of the preformed liposomes. Lecithin/cholesterol liposomes are prepared according to a membrane extrusion method using a commercially available apparatus (Avestin, Ottawa, Canada). Lecithin and cholesterol at a membrane-mimetic mole ratio, 7:3, are first coated onto the wall of a round bottom glass tube. The dry lipids are then dispersed in PBS using an ultrasonic water bath. Liposomes are produced by passing the lipid emulsion repeatedly through a polycarbonate membrane having pores 400 nm in diameter. The diameter of the liposomes is determined by the pore size of the membrane used during the extrusion method. Liposomes produced using this method are unilamellar. To 2.0 mL of PBS containing 40 mg of liposomes is added an equivalent volume of PBS containing 9.0 .mu.M fibrinogen. This mixture is then dispersed at room temperature continuously for 15 minutes using an ultrasonic waterbath. At the start of this sonication, 25 .mu.l of palmitoyl chloride dissolved in a equivalent volume of acetone is added slowly to the dispersion. Once coated with fibrinogen, the density of the liposomes increases appreciably, approaching that of fibrinogen. Consequently, the liposomes can be pelleted by centrifugation at 1500 g for 15 minutes and then washed with buffer to remove any unbound protein.

Current US Original Classification (1):

424/450

CLAIMS:

2. A liposome according to claim 1 which is formed from phospholipid materials selected from the group consisting of phosphatidylcholine, phosphatidic acid, lysophosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, sphingolipids, phosphatidylglycerol, sphingomyelin, cardiolipin, glycolipids, gangliosides, cerebrosides, and mixtures thereof.

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File: USPT

Nov 24, 1987

DOCUMENT-IDENTIFIER: US 4708861 A

TITLE: Liposome-gel compositions

Brief Summary Text (44):

In another embodiment of the present invention the liposome-gel preparation may be used in cell or tissue culture systems to provide for the prolonged release of the bioactive agent into the culture medium. The liposome-gel preparation may serve as a support for cell adhesion and growth; alternatively the liposome-gel preparation may be applied to the cell culture as an overlay.

Brief Summary Text (51):

Most amphipathic lipids may be constituents of SPLVs. Suitable hydrophilic groups include but are not limited to: phosphato, carboxylic, sulphato and amino groups. Suitable hydrophobic groups include but are not limited to: saturated and unsaturated aliphatic hydro-carbon groups and aliphatic hydrocarbon groups substituted by at least one aromatic and/or cycloaliphatic group. The preferred amphipathic compounds are phospholipids and closely related chemical structures. Examples of these include but are not limited to: lecithin, phosphatidyl-ethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, cardiolipin, phosphatidic acid and the cerebrosides. Specific examples of suitable lipids useful in the production of SPLVs are phospholipids which include the natural lecithins (e.g., egg lecithin or soybean lecithin) and synthetic lecithins, such as saturated synthetic lecithins (e.g., dimyristoylphosphatidylcholine, or dipalmitoylphosphatidylcholine or distearoyl-phosphatidylcholine) and unsaturated synthetic lecithins (e.g., dioleoylphosphatidylcholine or dilinoleoyl-phosphatidylcholine). The SPLV bilayers can contain a steroid component such as cholesterol, coprostanol, cholestanol, cholestane and the like. When using compounds with acidic hydrophilic groups (phosphato, sulfato, etc.) the obtained SPLVs will be anionic; with basic groups such as amino, cationic liposomes will be obtained; and with polyethylenoxy or glycol groups neutral liposomes will be obtained. The size of the SPLVs varies widely. The range extends from about 100 nm to about 10,000 nm (10 microns) and usually about 100 nm to about 1,500 nm. The SPLVs are characterized by a few to over 100 lipid bilayers enclosing aqueous compartments.

Brief Summary Text (59):

Specific examples of suitable lipids useful in the production of MPVs are phospholipids which include but are not limited to the natural lecithins or phosphatidylcholines (e.g., egg lecithin or soybean lecithin) and synthetic lecithins, such as saturated synthetic lecithins (e.g., dimyristoylphosphatidylcholine or dipalmitoylphosphatidylcholine or distearoylphosphatidylcholine) and unsaturated synthetic lecithins (e.g., dioleoylphosphatidylcholine or dilinoleoylphosphatidylcholine). Other phospholipids include but are not limited to phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, cardiolipin, phosphatidic acid, ceramides and the cerebrosides. The MPV bilayers can contain a steroid component such as cholesterol, coprostanol, cholestanol, cholestane and the like. When using compounds with acidic hydrophilic

groups (phosphato, sulfato, etc.) the obtained MPVs will be anionic; with basic groups such as amino, cationic liposomes will be obtained.

Brief Summary Text (75):

A number of researchers add "stabilizers" such as sterols, cholesterols and the like to the phospholipid bilayers in order to alter the permeability of the liposome (Papahadjopoulos, D., Kimilberg, H. K., 1974, in Progress in Surface Science, ed. S. G. Davison, pp. 141-232, Oxford: Pergamon; Demel, R. A., Bruckdorf, K. R., Van Deenan, L. L., 1972, Biochem. Biophys. Acta, 255:331-347). For the present invention it is important that the stable liposomes will release their contents upon contact with body fluids or culture media. For a particularly useful liposome preparation, see U.S. patent application Ser. No. 516,268, by Fountain, filed July 22, 1983, which describes liposome preparations containing a titratable agent incorporated into the membrane which allows for a controlled release of the liposome entrapped agent. Thus the rate of release may be controlled by modifying liposome membranes accordingly.

Brief Summary Text (87):

The liposome-gel preparations of the present invention may also be used in vitro to provide for sustained release of a bioactive agent into the cell or tissue culture medium. Such bioactive agents may include but are not limited to nutrients, drugs, hormones, growth factors, etc. The liposome-gel preparation may be used as a support for cell adhesion and growth; for instance, a liposome-collagen gel may be especially useful for culturing muscle cells, nerve cell, or liver cells. When the liposome-gel preparation is applied as an overlay, a liposome-agarose gel may be particularly useful.

Detailed Description Text (31):

Another liposome preparation (Table 4) contained fibronectin covalently crosslinked to lipids. The glycoprotein fibronectin which has high affinity for collagen was covalently cross-linked to the liposome bilayer by an enzyme catalyzed method described in U.S. patent application Ser. No. 533,583 by Weiner et al., filed Sept. 19, 1983. Briefly, ¹²⁵I-HGH/SPLVs were prepared as described Section 5.1 using egg PC and phosphatidylethanolamine (8:2 mole %) and Tris (tris (hydroxymethyl)aminomethane) saline buffer containing ¹²⁵I-HGH. In order to covalently link the fibronectin to the liposomes the ¹²⁵I-HGH/SPLV suspension was incubated for 2 hours at 37.degree. C. with 1 mg fibronectin (Seragen Inc., Boston, MA; or Collaborative Research Inc., Lexington, MA) in 1 ml Tris saline buffer with 20 mM CaCl₂, 100 μ g Factor XIII (trans-glutaminase, Alpha Therapeutic Corp., Los Angeles, CA); 1 unit thrombin (Sigma, St. Louis, MO). (One unit of thrombin will clot a 25 mg % fibronectin solutions in 15 seconds at 37.degree. C.). After incubation the fibronectin modified-SPLVs (¹²⁵I-HGH/FN-SPLVs) were pelleted at 10,000.times.g for 10 minutes, and washed 3 times.

Current US Cross Reference Classification (4):

424/450

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<u>L15</u>	L14 and 424/450.ccls.	87	<u>L15</u>
<u>L14</u>	L11 and adhesion	320	<u>L14</u>
<u>L13</u>	L12 and lyso\$	260	<u>L13</u>
<u>L12</u>	L11 and 424/450.ccls.	420	<u>L12</u>
<u>L11</u>	L10 and cholesterol	1225	<u>L11</u>
<u>L10</u>	L9 and phosphatidylserine	1225	<u>L10</u>
<u>L9</u>	L8 and phosphatidylethanolamine	1528	<u>L9</u>
<u>L8</u>	L7 and cholesterol	2236	<u>L8</u>
<u>L7</u>	(lecithin or phosphatidylcholine) same sphingomyelin	2983	<u>L7</u>
<u>L6</u>	(lecithin or phosphatidylcholine) same sphingomyelin same phopshatidylethanolamine	0	<u>L6</u>
<u>L5</u>	(lecithin or phosphatidylcholine) same sphingomyelin same phopshatidylethanolamine same cholesterol	0	<u>L5</u>
<u>L4</u>	(lecithin or phosphatidylcholine) same spingomyelin same phopshatidylethanolamine	0	<u>L4</u>

<u>L3</u>	(lecithin or phosphatidylcholine) same spingomyelin same phopshatidylethanolamine same cholesterol	0	<u>L3</u>
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<u>L1</u>	(lecithin or phosphatidylcholine) same spingomyelin same phopshatidylethanolamine same (phosphatidyl adj1 serine) same (phosphatidyl adj1 inositol) same cholesterol	0	<u>L1</u>

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(\$surgical adj1 adhesion) same (lecithin)	1

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<u>L3</u>	(\$surgical adj1 adhesion) same (lecithin or phospholipid)	13	<u>L3</u>
<u>L2</u>	(\$surgical adj1 adhesion) adj10 (lecithin or phospholipid)	4	<u>L2</u>
<u>L1</u>	(\$surgical adj1 adhesion) adj 10 (lecithin or phospholipid)	107732	<u>L1</u>

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liposome same (\$surgical adj1 adhesion)	21

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L1 liposome same (\$surgical adj1 adhesion)

21 L1

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(\$surgical adj1 adhesion) same cholesterol	14

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<u>L3</u>	(\$surgical adj1 adhesion) same cholesterol	14	<u>L3</u>
<u>L2</u>	liposome adj10 (cholesterol adj5 rigid\$)	29	<u>L2</u>
<u>L1</u>	liposome same (cholesterol adj5 rigid\$)	106	<u>L1</u>

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L2: Entry 74 of 74

File: USPT

Apr 29, 1997

DOCUMENT-IDENTIFIER: US 5624679 A

TITLE: Methods and compositions for poly-.beta.-1-4-N-acetylglucosamine biological barriers

Brief Summary Text (20):5.6.1.3. UTILIZING p-GlcNAc MATERIALS FOR THE PREVENTION OF POST-SURGICAL ADHESIONSBrief Summary Text (64):17. EXAMPLE: p-GlcNAc SUCCESSFULLY REDUCES AND PREVENTS POST-SURGICAL ADHESIONSBrief Summary Text (100):

Additionally, the present invention relates to the uses of the purified p-GlcNAc, its derivatives, and/or its reformulations. Among these uses are novel commercial applications relating to such industries as the biomedical, pharmaceutical, cosmetic and agricultural industries, all of which require starting materials of the highest degree of purity. For example, the p-GlcNAc materials of the invention may be formulated to exhibit controllable biodegradation properties, and, further, may be used as part of slow drug delivery systems, as cell encapsulation systems, and as treatments for the prevention of post-surgical adhesions; and for the induction of hemostasis. For example, the p-GlcNAc materials of the invention exhibit properties that make them ideally suited for a large number of biomedical applications. Some of these properties include but are not limited to: high purity and composition consistency; biocompatibility; controllable biodegradability; and, an ability to immobilize and encapsulate agents, such as therapeutic agents, and cells. These properties are useful, for example, in the formulation of biodegradable barrier devices, improved drug formulations and cell based therapeutics.

Brief Summary Text (101):

The biodegradable barriers of the invention include p-GlcNAc based materials used as devices, for example, as temporary barriers which become resorbed by the body. This category of products include, but is not limited to, devices that prevent the formation of surgical adhesions, stop bleeding, and promote wound healing. Such biodegradable barriers can further be used as surgical space fillers, periodontal barriers or for soft tissue augmentation.

Detailed Description Text (150):

Hormonal therapeutics can include, but are not limited to corticosteroids (cortisone acetate, hydrocortisone, prednisone, prednisolone, methyl prednisolone and dexamethasone), estrogens, (diethylstilbestrol, estradiol, esterified estrogens, conjugated estrogen, chlorotiasnene), progestins (medroxyprogesterone acetate, hydroxy progesterone caproate, megestrol acetate), antiestrogens (tamoxifen), aromatase inhibitors (aminoglutethimide), androgens (testosterone propionate, methyltestosterone, fluoxymesterone, testolactone), antiandrogens (flutamide), LHRH analogues (leuprolide acetate), and endocrines for prostate cancer (ketoconazole).

Detailed Description Text (178):5.6.1.3. UTILIZING p-GlcNAc MATERIALS FOR THE PREVENTION OF POST-SURGICAL ADHESIONSDetailed Description Text (179):

Additionally, p-GlcNAc membranes may be used to provide a biodegradable, biocompatible mechanical barrier to prevent post-surgical adhesions. The Example presented in Section 17, below, demonstrate such a p-GlcNAc application. Solid p-GlcNAc or p-GlcNAc derivatives formulated into membranes or sponges may be utilized for such an application. Preferred membranes are thin, generally less than about 1 mm in thickness. Preferable p-GlcNAc derivatives are p-GlcNAc derivatives which have been about 50-80% deacetylated. Such p-GlcNAc derivatives will generally be resorbed approximately 7-21 days post-implantation..

Detailed Description Text (180):

Liquid p-GlcNAc derivatives are also suitable for use in the prevention of post-surgical adhesions. Preferable liquid p-GlcNAc derivatives for such an application are deacetylated p-GlcNAc salt derivatives and carboxymethyl p-GlcNAc derivatives. A p-GlcNAc derivative which is particularly preferred for the prevention of post-surgical adhesions is a p-GlcNAc-lactate derivative, especially a p-GlcNAc-lactate gel derivative. As used herein, the term p-GlcNAc-lactate means that the lactic acid moiety is functionally attached to a partially or fully deacetylated poly-.beta.-1.fwdarw.4-N-acetylglucosamine of the invention. Such p-GlcNAc-lactate derivatives may be formulated using propylene glycol and water, as, for example, described in Section 17.1. p-GlcNAc-lactate derivatives may be produced having high and low viscosities, which allows for the ability to tailor the p-GlcNAc used to the specific indication of interest. For example, it may be useful to use a p-GlcNAc product having a lower viscosity for delivery through a syringe or via a spray, while it may be desirable to use a p-GlcNAc product having a higher viscosity, and therefore greater lubrication properties, when the indication is an orthopedic one.

Detailed Description Text (181):

For the prevention of post-surgical adhesions, solid p-GlcNAc formulations are suitable for clearly circumscribed wound sites. Such p-GlcNAc formulations should be applied following the surgical procedure and the material should completely cover the traumatized tissue. It can be applied either in conjunction with either general or minimally invasive (e.g., laparoscopic) surgical procedures. The solid p-GlcNAc formulations can be cut and applied using standard surgical procedures and instrumentation well known to those of skill in the art.

Detailed Description Text (182):

The liquid p-GlcNAc formulations can be applied, for the prevention of post-surgical adhesions, in larger areas prone to form such postoperative adhesions. The p-GlcNAc-lactate gel, for example, can be applied before the surgical procedure to provide additional lubrication and thus reduce the amount of traumatized tissue. Alternatively, the liquid p-GlcNAc formulation, such as p-GlcNAc-lactate, can be applied following the surgical procedure to form a physical barrier to prevent postoperative adhesion formation.

Detailed Description Text (184):

The amount of liquid p-GlcNAc formulation, such as the p-GlcNAc-lactate gel formulation, required for prevention of post-surgical adhesions is proportional to the extent of the traumatized tissue. The p-GlcNAc material administered should be applied in the range of 0.1 ml to 1.5 ml per sq. cm of surface area.

Detailed Description Text (185):

Various animal models which are known in the art can be used to test the post-surgical adhesion formulations of the invention. These include, but are not limited to, the Rat cecum model (Harris, E. W., et al., 1992, Journal of Investigative

Surgery, 5:260; and the Rabbit uterine horn model (Diamond, M. P., et al., 1987, Microsurgery, 8:197.

Detailed Description Text (350):

17. EXAMPLE: p-GlcNAC SUCCESSFULLY REDUCES AND PREVENTS POST-SURGICAL ADHESIONS

Detailed Description Text (351):

The Example presented herein demonstrates the successful use of p-GlcNac materials, specifically a p-GlcNac membrane and gel formulation, to reduce or prevent the formation of post-surgical adhesions in a series of animal models for such adhesions.

Detailed Description Text (360):

Specifically, the surgical procedure for inducing post-surgical adhesions in these rats involved the following. Animals were placed in dorsal recumbency and prepared and draped accordingly for aseptic surgery. Abdominal cavities were exposed through a midline incision. An area, approximately 0.5 cm.times.1.0 cm, of parietal peritoneum on the left abdominal wall was carefully excised, removing a thin layer of muscle, along with the peritoneum.

Detailed Description Text (364):

Fourteen days after surgery, animals were euthanized and the abraded area was examined for the formation of post-surgical adhesions. If adhesions were present, the entire area involved in the adhesion (i.e., body wall, test or control article, and internal organs) were dissected free of the animal.

Detailed Description Text (383):

Such adhesions, referred to as post-surgical adhesions, may produce pain, obstruction and malfunction by distorting the organ or organs involved. Immobilized joints, intestinal obstruction and infertility are often linked to the formation of post-surgical adhesions. Furthermore, post-surgical adhesion will complicate and extend the length of future surgical procedures in the surrounding region. This last issue is of particular relevance to open heart surgeries and cesarean section obstetrical procedures where additional surgeries may be required. The formation of adhesions is very common following abdominal, cardiovascular and orthopedic surgical procedures.

Detailed Description Text (384):

When adhesions become pathological and seriously interfere with organ function, surgical adhesiolysis (sharp or blunt dissection of the adhesion in conjunction with meticulous surgical techniques) is the treatment that is currently used to eliminate adhesions. In 1991, approximately 500,000 adhesiolysis procedures were performed in the U.S. This procedure is, however, notoriously ineffective, with the frequency of recurrence of adhesion formation reported to be as high as 90%. Further, no other technique or composition has proven effective in the prevention of such post-surgical adhesions.

Detailed Description Text (385):

The results presented herein, therefore, are significant in that they demonstrate the effectiveness of the p-GlcNac materials of the invention for the prevention of post-surgical adhesions. Specifically, the results presented here demonstrate the efficacy of p-GlcNac based solid and liquid formulations as barriers to the formation of abdominal post-surgical adhesions in accepted rat and pig animal model systems.

Detailed Description Text (388):

Partially deacetylated p-GlcNac membranes were also tested for their ability to reduce or prevent the occurrence of post-surgical adhesions in the rat animal model. A total of 22 rats were used in the study. 12 animals were used as controls, with 6 receiving no treatment and 6 receiving InterCEED.TM.. Ten animals each

received a 1 cm.times.1 cm membrane of an approximately 60% deacetylated p-glcNAc formulation. The animals which received the partially deacetylated p-GlcNAc membrane showed a significant reduction in the incidence of formation of postoperative adhesions, as compared with the non-treated controls and InterCEED.TM., as shown, below, in Table IX.

CLAIMS:

6. A method for reduction of post-surgical adhesions comprising: topically administering to a patient the biodegradable barrier-forming material of claim 1, 2 or 3 to a surgical site prior to performing a surgical procedure, so that lubrication is provided and surgical trauma to tissue is reduced.

7. A method for reduction of post-surgical adhesions comprising: topically administering to a patient the biodegradable barrier-forming material of claim 4 or 5 to a surgical site prior to performing a surgical procedure, so that lubrication is provided and surgical trauma to tissue is reduced.

8. A method for reduction of post-surgical adhesions comprising: topically administering to a patient the biodegradable barrier-forming material of claim 1, 2 or 3 to a surgical site at the completion of a surgical procedure, so that a physical barrier between traumatized tissue and non-traumatized tissue is produced, thus reducing the occurrence of post-surgical adhesions.

9. A method for reduction of post-surgical adhesions comprising: topically administering to a patient the biodegradable barrier-forming material of claim 4 or 5, to a surgical site at the completion of a surgical procedure, so that a physical barrier between traumatized tissue and non-traumatized tissue is produced, thus reducing the occurrence of post-surgical adhesions.

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<u>L2</u>	(\$surgical adj1 adhesion) and (antiestrogen or anti\$estrogen)	74	<u>L2</u>
<u>L1</u>	(\$surgical adj1 adhesion) same (antiestrogen or anti\$estrogen)	0	<u>L1</u>

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